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EXAMINER	
PRIEBE,S	
ART UNIT	**PAPER NUMBER**
1632	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/464,767	Both et al.
Examiner	**Art Unit**
Scott D. Priebe, Ph.D.	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL.** 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☒ The proposed drawing correction filed on *May 16, 2001* is: a)☐ approved b)☒ disapproved.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some* c)☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *08/776,274*.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)

16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4

18)☐ Interview Summary (PTO-413) Paper No(s). _____

19)☐ Notice of Informal Patent Application (PTO-152)

20)☒ Other: *Notice to Comply with Sequence Rules*

DETAILED ACTION

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The specification to which the oath or declaration is directed has not been adequately identified. In the instance where an application filed under 37 CFR 1.53(b) is filed without a signed oath or declaration and such application is accompanied by an amendment, that amendment is considered a part of the original disclosure. A subsequently filed oath or declaration must refer to both the application and the amendment. See MPEP § 601.01(a); 608.04(b) 704.09.

Drawings

The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on 5/16/01 have been disapproved because they introduce new matter into the drawings. 37 CFR 1.121(a)(6) states that no amendment may introduce new matter into the disclosure of an application. The original disclosure does not support the showing of a sequence comprising the T residue inserted at position 24805. See the objection to the specification under 35 U.S.C. 132 *infra*. For this examination, claim 24 is interpreted as being directed to originally filed Figure 13.

Specification

The communication received on 5/16/01 is not fully responsive to the communication mailed 2/16/01 for the reason(s) set forth on the attached Notice to Comply With the Sequence Rules.

Since the response appears to be *bona fide*, but through an apparent oversight or inadvertence failed to provide a complete response, applicant is required to complete the response within a time limit set in this Office Action.

Applicants are required to comply with all of the requirements of 37 CFR 1.821 through 37 CFR 1.825. *Any* response to this Office Action which fails to meet *all* of these requirements will be considered non-responsive. The nature of the sequence disclosed in the instant application has allowed an examination on the merits, the results of which are communicated below.

The amendment filed 5/16/01 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The Sequence Listing filed 5/16/01 contains SEQ ID NO: 3 which is intended to be the sequence shown in original Figure 13. However, it is not identical to original Figure 13 at least as follows. An X in original Figure 13 appears at positions 1140 and 24848, which is absent in SEQ ID NO: 13. It is noted that the original specification provided no explanation as to the identity of

the nucleotides represented by an X. When addressing this issue, Applicant should takes steps to ensure that no new matter is introduced into the specification by the substitute Sequence Listing, where a nucleotide cannot be designated by X. Also, SEQ I D NO: 13 contains a T residue at position 24805 which was not present in originally filed Figure 13. Applicant's statement that the addition of the T residue at position 24805 corrects a typographical error is noted. However, this statement is not supported by any evidence, such as in the form of a declaration under 35 CFR 1.132 explaining *inter alia* the nature of the error, how it occurred, how it was discovered, and establishing a chain of custody between the originally disclosed subject matter and the subject matter newly added to the specification.

Applicant is required to cancel the new matter in the reply to this Office action.

The disclosure is objected to because of the following informalities: The brief description of Figure 13 inserted at page 8, line 27, is incomplete. Figure 13 shows that the nucleotide sequence is of plasmid pOAV100, which contains a modified OAV287 genome. Also, the sequence contains two X residues, and the description of the figure does not explain what the X means. In correcting the latter omission, no new matter should be introduced into the specification.

Appropriate correction is required.

Claim Objections

Claims 1-24 are objected to because of the following informalities: Each of claims 1-4, 7, 12-14, and 21 identifies the nucleotide sequence of OAV287 as "shown in Fig. 1". Claim 24 recites "the sequence set forth in Figure 13". Specific nucleic acid sequences referred to in a claim must be identified by the appropriate SEQ ID NO. It is suggested that "as shown in Fig. 1" be replaced with --as set forth in SEQ ID NO: 1--, assuming that SEQ ID NOs: 1 is identical to the sequences shown in Fig. 1. Claim 24 is problematic, since the sequence shown in original Figure 13 is not present in the current Sequence Listing, and SEQ ID NO: 3 is not identical to the sequence in Figure 13.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 8-11 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated DNA sequences comprising a nucleotide sequence identical to all or part of the nucleotide sequence of SEQ ID NO: 1 or of Figure 13 and variants of SEQ ID NO: 1 or of Figure 13 comprising nucleotide differences in the viral protein coding sequences that do not alter the amino acid sequence encoded thereby, does not reasonably

provide enablement for any other variants of the sequence set forth in SEQ ID NO: 1 or Figure 13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. It is noted that the specification discloses a few specific modifications to the OAV287 genome in order to remove or insert restriction sites for convenient manipulation wherein the changes had no discernible effect on function of the genome with respect to propagation of the virus or recombinant virus comprising a exogenous coding sequence. The specification also enables those specific embodiments of the claimed invention wherein the sequence differs from SEQ ID NO: 1 only with respect to these specific modifications and silent nucleotide differences that do not alter the amino acid sequences encoded.

The claims are drawn to isolated DNA molecules, including plasmids, that comprise a broadly recited genome of ovine adenovirus (OAV287) "substantially" as shown in Fig. 1 (SEQ ID NO: 1) or Fig. 13 or a functionally equivalent nucleic acid sequence. This broad recitation raises two issues of enablement; first with respect to the scope of "genome of ovine adenovirus (OAV287) substantially as shown in Figure 1", and second, with respect to the scope of "functionally equivalent nucleic acid sequences".

As indicated in the rejection *infra* under 35 USC 112, 2nd para., the scope of genome of ovine adenovirus (OAV287) "substantially" as shown in Figure 1 is unclear. The meaning of "substantially" in this context is unclear, and it has not been defined in the specification. Given that the metes and bounds of this element of the claim is unclear; one skilled in the art would not

be able to make any given ovine adenoviral genome that was "substantially as shown in Figure 1", but not identical to it, and be certain that the isolated DNA comprising it was embraced by the claimed invention. Therefore, it would take undue experimentation to make the isolated DNA (or plasmid) commensurate in scope with the claims.

The phrase "functionally equivalent nucleic acid sequence" has been defined in the specification on page 6, lines 3-12 as referring only to nucleotide sequence variations in OAV287 protein coding sequences that are silent, either because the nucleotide differences are in a wobble base positions such that the variant coding sequence encodes the same polypeptide as the sequence shown in Fig. 1 or Fig. 13, or if the variation leads to a new amino acid sequence, that the resulting polypeptide has the same biological activity as the polypeptide encoded by the OAV287 genome, i.e. a silent amino acid substitution. The specification does not enable one skilled in the art to make functionally equivalent nucleic acid sequences that encode a different polypeptide than does the sequence shown in Fig. 1 or Fig. 13.

The specification provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in any of the proteins or polypeptides encoded by the OAV287 genome that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the proteins. The specification also provides no working examples of nucleic acid sequences that are "functionally equivalent" to the OAV287 genome. It is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids

that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Also, as admitted in the specification at pages 15-17, little if any amino acid sequence identity was observed for polypeptides encoded by the OAV287 genome and the genomes of adenoviruses. Therefore, comparison to other known adenoviral coding sequences is no help. Consequently, excessive trial and error experimentation would be required to identify the necessary nucleic acid sequence variations encoding a biologically active proteins with amino acid sequences differing from that encoded by SEQ ID NO: 1 since the amino acid sequence of such polypeptides could not be predicted *a priori.*

As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic

sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only a single nucleic acid sequence, SEQ ID NO: 1, for the OAV287 genome and does not identify the expressed open reading frames (as opposed to predicted ORFs or the amino acids encoded thereby; nor does it identify the functions of any proteins encoded or any assays by which function of protein variants could be assessed. In light of the lack of working examples and guidance on amino acid sequence variations that do not affect the biological activity of the polypeptides encoded by the disclosed sequence, the unpredictability of predicting such variants as disclosed by the prior art, and the excessive trial and error experimentation that would be required to practice the invention commensurate in scope with the claims, it would require undue experimentation to make isolated DNA molecules throughout the claimed scope of the invention.

Claims 4-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to isolated DNA molecules that comprise at least a 15 nucleotide nucleic acid sequence that is "substantially unique" to the OAV287 genome. The specification defines "substantially" in terms of high stringency hybridization, which makes no sense in the

context of "is unique". No definition is supplied for "is substantially unique", so the metes and bounds of the at least 15 nucleic acid base sequence are unclear in this respect. It is unclear whether "substantially unique" means that the at least 15 nucleotide sequence is not found in any other non-OAV287 DNA molecule, other than the OAV287 genome, regardless of origin, e.g. in nature or man-made, or found in some low unspecified fraction of other non-OAV287 DNA molecule. Consequently, "substantially unique to the ovine adenovirus (OAV287)" is interpreted as meaning that the at least 15 nucleic acid base sequence present in the claimed DNA molecule is unique to OAV287, and found in no other non-OAV287 derived DNA molecule, whether natural or man-made. The specification does not provide any guidance for identifying which of the over 29,500 possible sequences of 15 nucleotides or more from the OAV287 genome are unique to the OAV287 nor does it identify any such 15 nucleotide sequences.

The only prior art methods of determining whether a given 15-mer is unique to OAV287 would be to compare the sequence of each possible 15 nucleotide sequence of the OAV287 genome to the sequences of all nucleic acids that exist, not just those known, or to use each possible at least 15 base oligonucleotide present in the OAV287 genome as a hybridization probe against samples of all DNA molecules in existence, not just those known. The latter method is unpredictable to the extent that hybridization conditions for detecting a perfect match to oligonucleotides as short as 15 nucleotides is unpredictable. As disclosed in Wallace et al. (Methods Enzymol. 152: 432-442, 1987) oligonucleotides, particularly those of 14 nucleotides or less, tend to bind nonspecifically under conditions that do not favor hybridization only between

perfectly matching sequences (see para. bridging pages 433-34). Although hybridization conditions that favor hybridization of only perfectly matching sequences can be approximated mathematically, the actual conditions must be determined empirically, (see Sambrook et al. Molecular Cloning, A Laboratory Manual, 2nd ed., 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, p. 11.47). Therefore, different hybridization conditions would need to be determined for each of the possible 15-mers. Since not all possible nucleic acid molecules in existence have been isolated, yet alone sequenced, it would be an almost insurmountable task to identify even a single "at least 15 nucleic acid base sequence" of the OAV287 genome that was unique, let alone all of the claimed sequences commensurate in scope with the claims. An excessive amount of experimentation would be required to isolate all DNA molecules and then to either determine the sequence of each existing DNA molecule or to hybridize each possible 15-mer of the OAV287 genome to samples of all DNA molecules in existence, which would include empirically determining the appropriate hybridization conditions for over 29,500 different probes. A word search using a 15 nucleotide window of the GenBank/EMBL databases was conducted by the PTO on 6/24/98 and revealed that the databases contained 146,914 hits for 15-mers present in SEQ ID NO: 1, or approximately five hits per possible 15-mer in SEQ ID NO: 1. This result suggests that many if not most of the possible 15 nucleotide sequences present in the OAV287 genome are not unique to OAV287 based just on the small fraction of sequences in existence disclosed in the databases.

In addition, claims 5 and 6 are limited to 15 nucleic acid base sequences that are present in "functional elements" of the OAV287 genome, e.g. inverted terminal repeats (ITRs), promoters, genes, the packaging sequence and RNA processing signals. The specification presents the nucleotide sequence of the OAV287 genome. The specification identifies the 46 nucleotide ITRs, the location in the nucleotide sequence of the major late promoter (MLP) and tripartite leader sequence (TLS), provides a map of putative open reading frames (ORFs), but does not define the ORFs in terms of the nucleotide sequence or disclose whether the ORFs detected in the sequence represent proteins that are actually expressed from OAV287 DNA. The specification does not disclose any other "functional elements", although certainly more are to be expected such as the packaging signal and promoters for other ORFs than the MLP, nor does it disclose guidance on identifying them. The specification teaches that based on nucleotide and amino acid sequence identity OAV287 "shows major structural and sequence variations compared with all other adenoviruses studied to date". To summarize: no homology to any E1A ORF was detected either for the nucleotide sequence or predicted amino acid sequence; the E4 region was not located at the right-hand end of OAV287, and was tentatively assigned on the basis of a short predicted amino acid sequence motif present in one E4 protein of other adenoviruses; no obvious E3 region was identified, and the right hand end of OAV287 comprises ORFs of unknown function or relationship to other adenoviruses, which was tentatively called the E3 region in OAV287; an AT-rich region of unknown function and with no counterpart in other characterized adenoviruses was identified between the tentative E4 and E3 regions of OAV287; and no obvious homology was

detected for non-coding regions of OAV287 compared to other adenoviruses (see pages 15-17 of the specification). Thus, there is insufficient sequence identity between OAV287 and other well-characterized adenoviruses to allow any assignment of "functional elements" based on well-characterized adenoviral genomes. Thus, to practice the invention commensurate in scope with the specification, the skilled artisan would be required to engage in excessive experimentation including extensive genetic and mutational analysis, isolation and identification of proteins and mRNA transcripts, including splice variants, in order to identify the various functional elements present in OAV287 that are not disclosed in the specification. There is no *a priori* method for predicting their identity due to the extreme nucleotide and amino acid sequence divergence between OAV287 and the well-characterized adenoviruses. Such experimentation is undue.

In view of the lack of guidance and working examples for the identity of at least 15 nucleic acid base sequences that are unique to the OAV287 genome, the limited sample of functional elements identified in specification, the lack of guidance for identifying other functional elements, the unpredictability involved in identifying at least 15 nucleic acid base sequences that are unique to OAV287, especially since most existing nucleic acid sequences are unknown and unavailable, or identifying other functional elements, and the incredible amount of experimentation that would be required to overcome these deficiencies, it would require undue experimentation to practice the invention claimed.

Claims 3, 12-17, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for OAV287 vectors comprising all of the nucleotide sequence of SEQ ID NO: 1 and variants of SEQ ID NO: 1 comprising silent nucleotide differences in the viral protein coding sequences of SEQ ID NO: 1 that do not alter the amino acid sequence encoded thereby and methods of using such vectors for transferring heterologous DNA to cultured mammalian cells, does not reasonably provide enablement for any other variants of the sequence set forth in SEQ ID NO: 1, especially with respect to parts of the complete genome less than the whole and methods of transferring heterologous DNA to non-mammalian cells or to cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 18-20 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

For claims 3, 12-17, 21 and 22, it is noted that the specification discloses a few specific modifications to the OAV287 genome in order to remove or insert restriction sites for convenient manipulation wherein the changes had no discernible effect on function of the genome with respect to propagation of the virus or recombinant virus comprising a exogenous coding sequence. The specification also enables those specific viral vectors wherein the sequence differs

from SEQ ID NO: 1 only with respect to these specific disclosed modifications and as well as silent nucleotide differences that do not alter the amino acid sequences encoded.

Claims 3, 12-23 are drawn to an isolated DNA molecule (claim 3) or viral vectors that comprise a broadly recited genome of ovine adenovirus (OAV287) "substantially" as shown in Fig. 1 (SEQ ID NO: 1) or a functionally equivalent nucleic acid sequence or "portion thereof" and an exogenous nucleotide sequence that encodes either a non-adenoviral polypeptide or a "functional RNA" such as an mRNA, a ribozyme or anti-sense RNA; as well as methods of transferring the exogenous nucleotide sequence to an unspecified cell or to a cell in an unspecified animal using the viral vector. This broad recitation raises several issues of enablement.

The first issue concerns the scope of "genome of ovine adenovirus (OAV287) substantially as shown in Figure 1". As indicated in the rejection *infra* under 35 USC 112, 2nd para., the scope of genome of ovine adenovirus (OAV287) "substantially" as shown in Figure 1 is unclear. Given that the metes and bounds of this element of the claim is unclear; one skilled in the art would not be able to make any given ovine adenoviral genome that was "substantially as shown in Figure 1", but not identical to it, and be certain that the isolated DNA comprising it was embraced by the claimed invention. Therefore, it would take undue experimentation to make the viral vectors commensurate in scope with the claims.

Second, the phrase "functionally equivalent nucleic acid sequence" has been defined in the specification on page 6, lines 3-12 as referring only to nucleotide sequence variations in OAV287 protein coding sequences that are silent, either because the nucleotide differences are in a wobble

base positions such that the variant coding sequence encodes the same polypeptide as the sequence shown in Fig. 1, or if the variation leads to a new amino acid sequence, that the resulting polypeptide has the same biological activity as the polypeptide encoded by the OAV287 GENOME. The specification does not enable one skilled in the art to make functionally equivalent nucleic acid sequences that encode a different polypeptide than does the sequence shown in Fig. 1.

The specification provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in any of the proteins or polypeptides encoded by the OAV287 genome that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the proteins. The specification provides no working examples of nucleic acid sequences that are "functionally equivalent" to the OAV287 genome. It is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Also, as admitted in the specification at pages 15-17, little if any amino acid sequence identity was observed for polypeptides encoded by the OAV287 genome and the genomes of adenoviruses. Therefore, comparison to other known adenoviral coding sequences is no help. Consequently, excessive trial and error experimentation

would be required to identify the necessary nucleic acid sequence variations encoding a biologically active proteins with amino acid sequences differing from that encoded by SEQ ID NO: 1 since the amino acid sequence of such polypeptides could not be predicted *a priori*.

As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only a single nucleic acid sequence, SEQ ID NO: 1, and does not identify the open reading frames or the amino acids encoded thereby. In light of the lack of working examples and guidance on amino acid sequence variations that do not affect the biological activity of the polypeptides encoded by the

disclosed sequence, the unpredictability of predicting such variants as disclosed by the prior art, and the excessive trial and error experimentation that would be required to practice the invention commensurate in scope with the claims with respect to functionally equivalent nucleic acid sequences, it would require undue experimentation to make isolated DNA molecules throughout the claimed scope of the invention.

A third issue concerns isolated DNA molecules and viral vectors comprising only "part of" the OAV287 genome, such as the isolated DNA molecule or vectors comprising a deletion of sequences "not essential for the maintenance or viability of the native adenovirus". The specification does not provide any working examples of OAV287-based vectors that comprise deletions of more than a few nucleotides where restriction sites were removed or inserted that were maintained and viable, and little guidance as to what portions are "not essential for the maintenance or viability of the native adenovirus". What guidance is provided is based on speculation as to the identity of sequences present in OAV287 with no clear counterpart in any other adenovirus, such as the AT-rich region and the putative E3 region. The specification discloses that a single, small, specific insertion into the putative E3 region of OAV287 interrupted an ORF but did not impair the maintenance or viability of the virus. As discussed in more detail in the preceding rejection of claims 4-7, the specification teaches that OAV287 is quite different in terms of both structural and sequence similarity, with very few clear correlations between the well-characterized adenoviruses and OAV287. At the stage of characterization of OAV287 disclosed, one skilled in the art would be unable to predict which sequences of OAV287 could be

deleted without impairing maintenance or viability of the virus. This could only be determined by extensive trial and error, mutational analysis to determine empirically which parts of the OAV287 genome are dispensable. Therefore, in light of the minimal guidance and lack of working examples in the specification of OAV287-based vectors lacking regions "not essential for the maintenance or viability of the native adenovirus"; the extreme structural and sequence dissimilarity between OAV287 and the well-characterized adenoviruses; the unpredictability of identifying such dispensable regions *a priori*; and the excessive experimentation required to identify the dispensable regions *a posteriori;* it would require undue experimentation to make or use the invention wherein the viral vector was missing portions of its genome.

Claims 17-20 and 23 are drawn to methods of transferring an exogenous DNA sequence to an unspecified target cell (claim 17), which could include any prokaryotic or eukaryotic cell, either *in vitro* or *in vivo*, e.g. Eubacteria, archaebacteria, fungi, plants, protists, fish, worms etc., or a cell in an animal (claims 18-20 and 23) which could include anything from nematodes and other invertebrate animals to fish, mammals and other vertebrates. Mammalian adenoviruses, such as OAV287 and human adenovirus (HAV) types 2 and 5, are fairly host specific with respect to infection and propagation, although the ability to propagate in a given mammalian cell is not germane here. The ability of an adenovirus to infect a given host cell depends on the presence of membrane proteins on the target cell to which proteins exposed on the surface of the viral particle can bind. The specification shows that OAV287 can at least infect mammalian cells of non-ovine origin, but provides no working examples of or guidance for infecting target cells that are non-

mammalian. While the prior art discloses that adenoviral vectors based on HAV types 2 and 5 are able to infect cells of a variety of different mammals, it is silent on whether mammalian adenoviruses are able to infect non-mammalian cells. Consequently, one skilled in the art would be unable to predict whether or not an OAV287 vector would be able to infect a non-mammalian cell, especially cells that are not from animals or are distantly related to mammals.

With respect to *in vivo* use in delivering exogenous DNA to unspecified target cells in multicellular organisms or cells in animals, the specification teaches that these vectors are primarily for use in grazing animals, presumably this means grazing mammals, for the purpose of vaccination, gene therapy, or genetic engineering to promote growth or modify production traits. The specification provides little or no guidance concerning the target animal, the route of administration, the dose and time course of treatment, and successful treatment endpoints. With the exception of antigenic proteins and peptides for vaccines, the specification provides no guidance on what types of coding sequences, antisense sequences or ribozymes should be encoded by the exogenous DNA sequence present in the viral vectors used. The specification provides no working examples of any of these uses. The specification does present evidence that the vector lacking an exogenous DNA sequence can infect and propagate in sheep.

The prior art shows that adenoviral vectors, particularly those based on HAV types 4, 5 and 7 have been used to generate full or partial protective immunity in a variety of for varying lengths of time in a variety of non-human mammals against rabies, hepatitis B, vesicular stomatitis virus, herpes simplex virus and Epstein Barr virus. See Imler (Vaccine 13(13): 1143-1151, 1995),

which reviews the state of the prior art on adenoviral vector-based vaccines. Surprisingly, however, an HAV type 7 recombinant viral vector that could induce protective immunity to hepatitis B in chimpanzees, did not even result in the production of antibodies against the HBsAg expressed from the vector in humans (see Imler, page 1147, col. 2), showing some unpredictability with respect to the target mammal (note that this result was originally published in 1992, see Ref. 54 in Imler). Also, as discussed above the specification shows that based on the dramatic structural and sequence dissimilarity between the OAV287 genome and the genomes of other well-characterized mammalian adenoviruses, OAV287 is quite a different virus than the HAV viruses on which the prior art adenoviral vaccines are based. Therefore, one cannot predict whether OAV287-based vectors would be suitable substitutes for the prior art HAV-based vectors of the prior art vaccines.

Concerning the use of the viral vectors to deliver exogenous DNA encoding products that are therapeutic, promote growth or modify production characteristics, which presumably includes polypeptides, antisense RNA and ribozymes, this art area is poorly developed and highly unpredictable. Numerous problems have been encountered which have not been shown to be overcome by routine experimentation. These include the fate of the vector (volume of distribution, rate of clearance into the tissues, rate of elimination of the vector, etc.), *in vivo* consequences of altered gene expression and protein function, the trafficking of the genetic material within the various compartments of the cell, rate of DNA degradation, amount and stability of the mRNA produced, amount and stability of the protein produced, and the

compartmentalization of the protein produced. These factors differ significantly depending on the vector used, the protein produced and the effect desired or disease being treated. Orkin et al. ("Report and recommendations of the panel to assess the NIH investment in research on gene therapy", issued by the U.S. National Institutes of Health, 1995) reviews the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). It also discloses that adenoviruses are highly immunogenic, as are current vectors derived from them (page 8, para. 3), and that high immunogenicity of a viral vector may curtail long term expression and prohibit repeat administration, and that resulting counter-selection of infected cells by the immune system may contribute to lower transduction efficiencies and short-lived expression of the transgenes that has been observed (page 31, full para. 5).

In the case of antisense or ribozyme RNAs, Gewirtz et al. (Proc. Natl. Acad. Sci. USA, 93: 3161-3163, 1996) in discussing anti-mRNA methods involving antisense and ribozyme disclosed that these methods are highly variable in efficiency. The reference teaches that for a given antisense or ribozyme oligonucleotide to work in a cell, it must hybridize to an accessible RNA sequence, with sequence accessibility dependent on mRNA physical structure which is dependent upon both the primary sequence and associated proteins present in a living cell. Structure prediction of RNA has been "fraught with difficulty". Therefore, identification of a useful antisense or ribozyme oligonucleotide is a "hit or miss process" involving many experiments in which a given oligonucleotide has no effect. (see Gewirtz et al., page 3161, col. 2-3). James (Antiviral Chemistry & Chemotherapy, 2(4): 191-214, 1991) teaches that suitable antisense molecules cannot be predicted based on the primary sequence of an mRNA target (see page 198, col. 1). Christofferson et al. (J. Med. Chem. 38(12): 2023-2037, 1995) disclosed that even after the instant invention was made, that viral delivery of ribozymes and other oligonucleotides is at an early stage of development, mostly with retroviral vectors, and that more experience with them was needed, and that the problems are those common to gene therapy (page 2029, col. 2, 1st full para.). The specification does not address solutions to any of the problems that have been plaguing the art of gene therapy, and antisense and ribozyme therapy.

Given little or no guidance on *in vivo* applications in the specification and the lack of working examples, the high unpredictability of the art of *in vivo* DNA transfer in general with respect to the disclosed gene therapy and genetic engineering uses thereof, and the excessive

amount of non-routine experimentation it would require to overcome the known problems of gene therapy and the unpredictable problems associated with a new, untried vector (including using the vectors for vaccines) it would require undue experimentation to practice the invention *in vivo*.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-23 are indefinite for recitation of "a nucleotide sequence encoding the genome of ovine adenovirus (OAV287) substantially the same as shown in Figure 1" in claims 1-3, 12-14 and 21. First, "a nucleotide sequence encoding the genome" is incorrect word usage, since the nucleotide sequence would not "encode" the genome, it would be the genome. Technically, it is polypeptides that are encoded by nucleic acids.

Second, it is unclear what "ovine adenovirus (OAV287)" means due to the enclosure of OAV287 within parentheses. Does this phrase refer only to OAV287 or does "(OAV287)" intended to indicate that OAV287 is an example of an "ovine adenovirus". If the latter, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set

forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Third, the metes and bounds of "substantially the same as shown in Figure 1" are unclear. The specification has been amended to provide a definition of "substantially"; however, this does not clarify the meaning of this phrase as explained below. It is also unclear in what way a genome is "substantially the same" as another genome; substantially the same chemical composition or substantially the same sequence or some other relationship. It is suggested that "a nucleotide sequence encoding the genome of ovine adenovirus (OAV287) substantially the same as shown in Figure 1" be replaced with -- the genome of ovine adenovirus OAV287 as set forth in SEQ ID NO: 1--. If it is desired to include those specific variants disclosed in the specification wherein nucleotides were deleted to ablate a restriction site or insert a new one, they should be recited individually in alternative form.

Claims 4-6 are indefinite for recitation of "substantially unique" in claim 4. The meaning of "substantially" in this context is unclear, and the specification does not define "substantially

unique". Thus the metes and bounds of the "15 nucleic acid base sequence" are unclear. Either the sequence is unique or it is not.

Claim 9 recites the limitation "the adenoviral genome or a portion thereof" in lines 3-4. There is insufficient antecedent basis for "portion thereof" in the claim due to the amendment removing dependence on claim 3.

Claim 16 recites the limitation "the *Taenia ovis* 45W antigen" and "the PM95 antigen" in lines 4-5. There is insufficient antecedent basis for this limitation in the claim. In both cases, "the" should be deleted.

The specification has been amended to define "substantially" as used in the specification as meaning "a sequence which will hybridize to the specified sequence under conditions of high stringency". However, the word "substantially" is an adverb meaning really, actually, truly, or essentially. It is not a noun, such as "a sequence". While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). In addition, the word "substantially" is used in multiple contexts in the specification and claims for which the definition in the specification makes no sense. For example, claim 4 recites "is substantially unique to", as used in this context, the definition makes no sense when "substantially" is used to modify "is unique"; particularly when a fragment of SEQ ID NO: 1 that hybridizes to a different nucleic acid under high stringency conditions would clearly indicate that the fragment was NOT unique to OAV287. Also, the specification at page 6, lines 3-12, defines "functionally equivalent nucleic

acid sequence" as meaning, in part, altered nucleic acid sequences which encode a different amino acid sequences, but where the amino acid differences "do not substantially effect the biological activities" of the polypeptide. In this context, the definition of "substantially" makes no sense.

acid sequence" as meaning, in part, altered nucleic acid sequences which encode a different amino acid sequences, but where the amino acid differences "do not substantially effect the biological activities" of the polypeptide. In this context, the definition of "substantially" makes no sense.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

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Art Unit 1632

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [ ] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: Sequence Listing incomplete (two amino acid sequences p. 16, l. 6), and introduces new matter.

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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